[Version 8.1,01/2017]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PERMAWAY 600 mg intramammary suspension for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each intramammary syringe (3.6 g) contains:

Active substance:

Cloxacillin (as benzathine)…. 600 mg

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Intramammary suspension.
Shiny white to off-white viscous suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Dairy cattle (dry cows).

4.2 Indications for use, specifying the target species

For the treatment of subclinical mastitis at dry-off and prevention of new intramammary infections occurring during the dry period, caused by *Trueperella pyogenes, Staphylococcus spp., Streptococcus agalatiae, Streptococcus dysgalactiae* and *Streptococcus uberis*, susceptible to cloxacillin.

4.3 Contraindications

Do not use in cases of known hypersensitivity to penicillins, cephalosporins, or to any of the excipients. Do not use in cows with clinical mastitis outside the dry period.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

This product does not contain any antimicrobial preservatives.

Special precautions for use in animals

Use of the product should be based on susceptibility testing of bacteria isolated from milk samples obtained from the udder quarter(s) of each cow to be dried off. If this is not possible, therapy should be based on local (regional, farm level) risk based epidemiological information about the expected pathogen challenge, and susceptibility of target bacteria.

Use of the product deviating from the instructions given in the SPC may contribute to the development of bacterial resistance to cloxacillin which may also decrease the effectiveness of treatment with other beta-lactamase resistant penicillins. Dry cow therapy protocols should take local and national policies on antimicrobial use into consideration, and undergo regular veterinary review.

The feeding of waste milk containing residues of cloxacillin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

The efficacy of the product has only been established for target organisms listed in section 4.2.
Consequently, the occurrence of a severe mastitis after drying-off (sometimes fatal) due to other organisms, especially *Pseudomonas aeruginosa*, is possible. To reduce this risk it is important to observe strict aseptic technique for the administration of the product.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reactions to cephalosporins and vice versa. Allergic reaction to these substances may occasionally be serious.

People with known hypersensitivity to penicillins or cephalosporins should avoid any contact with the veterinary medicinal product.

Handle this product with great care to avoid exposure. Wear gloves during administration of the product and wash hands after use.

In case of accidental contact with skin or eyes, wash immediately with clean water.

If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

4.6 Adverse reactions (frequency and seriousness)

Immediate allergic reactions have been described in some animals (agitation, tremor, edema of the udder, eyelids and lips) which can lead to the death of the animals.

4.7 Use during pregnancy, lactation or lay

Do not use this medicinal product in the lactating cows.
The product is intended to be used during gestation. The safety of the medicinal product in dairy cows during gestation has not been shown. However, the amounts of cloxacillin absorbed by the intramammary route being low, the use of this drug during gestation does not pose any particular problem.

4.8 Interaction with other medicinal products and other forms of interaction

The safety of the concomitant use of this medicinal product with other intramammary medicinal products has not been established, so simultaneous use is discouraged.

4.9 Amounts to be administered and administration route

For single intramammary use

600 mg of cloxacillin i.e. the content of one syringe should be infused once into each quarter via the teat canal immediately after the last milking of the lactation.

Milk out thoroughly before starting administration. Before administering the medicinal product, the teats should be thoroughly cleaned and disinfected, and care should be taken to avoid contamination of the syringe nozzle. Administer the full content of a syringe in each quarter. Massage after administration. After administration it is recommended to immerse the teat in an approved disinfectant bath. Do not milk after treatment.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

No adverse reactions are expected in case of accidental overdose.

4.11 Withdrawal period(s)

Meat and offal: 28 days
Milk: Interval between treatment and calving is 42 days or longer: 4 days after calving.
Interval between treatment and calving is less than 42 days: 46 days after treatment.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: beta-lactam antibacterials, penicillins, for intramammary use.
ATCvet code: QJ51CF02.

5.1 Pharmacodynamic properties

Cloxacillin is a beta-lactamase resistant penicillin antibiotic with antibacterial activity. Its antibacterial effects target bacterial cell wall synthesis. Cloxacillin impairs the development of the bacterial cell wall by interfering with transpeptidases, the enzymes responsible for the cross-linkage of peptidoglycans chains, resulting in osmotic lysis of the cell wall.

Cloxacillin shows *in vitro* activity against Gram-positive bacteria, including *Staphylococcus* spp., *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus uberis* and *Trueperella pyogenes (formerly known as Arcanobacterium pyogenes* or *Corynebacterium pyogenes or Actinomyces pyogenes)*.
Escherichia coli is not susceptible to cloxacillin.

The following MIC (VetPath) of cloxacillin against mastitis pathogens have been described:

Bovine mastitis bacteria	**MIC_{50}** (µg/mL)	**MIC_{90}** (µg/mL)
Staphylococcus aureus	0.25	0.5-1
Streptococcus agalactiae	1	2
Streptococcus dysgalactiae	0.06-0.125	0.12-0.25
Streptococcus uberis	0.5-2	4
Trueperella pyogenes	0.25	2

The main resistance mechanism to cloxacillin was described in Staphylococci, notably in methicillin resistant isolates and is due to the production of the penicillin binding protein 2a (PBP2a) which has low affinity to the majority of β-lactams. PBP2a gene is harboured by the mobile genomic island SCC**mec** (staphylococcal cassette chromosome mec) which can carry resistance genes to other classes of antibiotics.

5.2 Pharmacokinetic particulars

Intramammary administration of cloxacillin benzathine results in negligible systemic absorption of the active substance. The small fraction of cloxacillin that reaches the systemic circulation is excreted mainly via the kidneys (and to a lesser extent via the bile duct).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stearic Acid
Aluminium Stearate
Liquid Paraffin

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: use immediately.

6.4. Special precautions for storage

Do not store above 25°C.

6.5 Nature and composition of immediate packaging

Low density polyethylene (LDPE) white intramammary syringe with a LDPE cap and a LDPE plunger.

Pack sizes:
Cardboard box of 24 intramammary syringes.
Cardboard box of 48 intramammary syringes.
Cardboard box of 96 intramammary syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box (24 intramammary **syringes, 48** intramammary **syringes, 96** intramammary **syringes)**

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PERMAWAY 600 mg intramammary suspension for cattle
Cloxacillin (benzathine)

2. STATEMENT OF ACTIVE SUBSTANCES

Cloxacillin (as benzathine) 600 mg /intramammary syringe

3. PHARMACEUTICAL FORM

Intramammary suspension

4. PACKAGE SIZE

24 intramammary syringes
48 intramammary syringes
96 intramammary syringes

5. TARGET SPECIES

Dairy cattle (dry cows)

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For single intramammary use.

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Meat and offal: 28 days
Milk: Interval between treatment and calving is 42 days or longer: 4 days after calving.
Interval between treatment and calving is less than 42 days: 46 days after treatment.

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once opened use immediately

11. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

intramammary **Syringe of 3.6 g**

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PERMAWAY 600 mg intramammary suspension for cattle
Cloxacillin (benzathine)

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Cloxacillin (as benzathine) 600 mg / intramammary syringe

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

3.6 g

4. ROUTE(S) OF ADMINISTRATION

Single intramammary use

5. WITHDRAWAL PERIOD(S)

Meat and offal: 28 days
Milk: Interval between treatment and calving is 42 days or longer: 4 days after calving.
Interval between treatment and calving is less than 42 days: 46 days after treatment.

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}
Once opened use immediately.

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:
PERMAWAY 600 mg intramammary suspension for cattle

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder and manufacturer responsible for batch release:
Vetoquinol Biowet Sp. z o.o**.**
ul. Kosynierów Gdyńskich 13-14 66-400 Gorzów Wlkp.
POLAND

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

PERMAWAY 600 mg intramammary suspension for cattle
Cloxacillin (benzathine)

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each intramammary syringe (3.6 g) contains:

Active substance:
Cloxacillin (as benzathine) 600 mg

Excipients, q.s.

Intramammary suspension
Shiny white to off-white viscous suspension.

4. INDICATION(S)

For the treatment of subclinical mastitis at dry-off and prevention of new intramammary infections occurring during the dry period, caused by *Trueperella pyogenes*, *Staphylococcus spp.*, *Streptococcus agalatiae*, *Streptococcus dysgalactiae* and *Streptococcus uberis*, susceptible to cloxacillin.

5. CONTRAINDICATIONS

Do not use in cases of known hypersensitivity to penicillins, cephalosporins, or to any of the excipients. Do not use in cows with clinical mastitis outside the dry period.

6. ADVERSE REACTIONS

Immediate allergic reactions have been described in some animals (agitation, tremor, edema of the udder, eyelids and lips) which can lead to the death of the animals.

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

7. TARGET SPECIES

Dairy cattle (dry cows)

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

For single intramammary use.
600 mg of cloxacillin i.e. the content of one syringe should be infused once into each quarter via the teat canal immediately after the last milking of the lactation.
Milk out thoroughly before starting administration. Before administering the medicinal product, the teats should be thoroughly cleaned and disinfected, and care should be taken to avoid contamination of the syringe nozzle. Administer the full content of a syringe in each quarter. Massage after administration. After administration it is recommended to immerse the teat in an approved disinfectant bath. Do not milk after treatment.

9. ADVICE ON CORRECT ADMINISTRATION

None.

10. WITHDRAWAL PERIOD(S)

Meat and offal: 28 days
Milk: Interval between treatment and calving is 42 days or longer: 4 days after calving.
Interval between treatment and calving is less than 42 days: 46 days after treatment.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not store above 25°C.
Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP.
The expiry date refers to the last day of that month.
Shelf life after first opening the container: use immediately.

12. SPECIAL WARNING(S)

Special precautions for use in animals:
Use of the product should be based on susceptibility testing of bacteria isolated from milk samples obtained from the udder quarter(s) of each cow to be dried off. If this is not possible, therapy should be based on local (regional, farm level) risk based epidemiological information about the expected pathogen challenge, and susceptibility of target bacteria.

Use of the product deviating from the instructions given in the package leaflet may contribute to the development of bacterial resistance to cloxacillin which may also decrease the effectiveness of treatment with other beta-lactamase resistant penicillins. Dry cow therapy protocols should take local and national policies on antimicrobial use into consideration, and undergo regular veterinary review.

The feeding of waste milk containing residues of cloxacillin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

The efficacy of the product has only been established for target organisms listed in the indications.
Consequently, the occurrence of a severe mastitis after drying-off (sometimes fatal) due to other organisms, especially *Pseudomonas aeruginosa*, is possible. To reduce this risk it is important to observe strict aseptic technique for the administration of the product.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross-reactions to cephalosporins and vice versa. Allergic reaction to these substances may occasionally be serious.

People with known hypersensitivity to penicillins or cephalosporins should avoid any contact with the veterinary medicinal product.

Handle this product with great care to avoid exposure.
Wear gloves during administration of the product and wash hands after use.

In case of accidental contact with skin or eyes, wash immediately with clean water.

If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips or eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

Pregnancy and lactation:
Do not use this medicinal product in the lactating cows.
The product is intended to be used during gestation. The safety of the medicinal product in dairy cows during gestation has not been shown. However, the amounts of cloxacillin absorbed by the intramammary route being low, the use of this drug during gestation does not pose any particular problem.

Interaction with other medicinal products and other forms of interaction:
The safety of the concomitant use of this medicinal product with other intramammary medications has not been established, so simultaneous use is discouraged.

Overdose (symptoms, emergency procedures, antidotes):
No adverse reactions are expected in case of accidental overdose.

Incompatibilities:
Not applicable.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15 OTHER INFORMATION

Pack sizes:
Cardboard box of 24 intramammary syringes.
Cardboard box of 48 intramammary syringes.
Cardboard box of 96 intramammary syringes.

Not all pack sizes may be marketed.